Opioid Use and Morbidities during Left Ventricular Assist Device Support

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Summary

The use of opioids during left ventricular assist device (LVAD) support is increasing, but the implication remains unknown. We investigated the association between the use of opioid and morbidities during LVAD supports. We retrospectively reviewed the clinical data of patients who received LVAD between 2014 and 2017, which were stratified by the use of opioid at post-LVAD 3 months. Among 136 patients, 77 (57%) were in the opioid group. Hemoglobin and albumin were lower, and C-reactive protein was higher at baseline and 3 months later in the opioid group ($P < 0.05$ for all). The opioid group displayed worse hemodynamics, with higher pulmonary capillary wedge pressure and central venous pressure ($P < 0.05$ for both). Furthermore, the opioid group had higher incidences of gastrointestinal bleeding (31% versus 17%, $P = 0.043$) and sepsis (30% versus 13%, $P = 0.036$) during the 1 year observational period, whereas survivals were not stratified by the use of opioid (83% versus 90%, $P = 0.27$). Opioid use was associated with morbidities accompanied by poor hemodynamics during LVAD supports. The detailed causality of opioid use on morbidities remains a future concern.

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The evolution in advanced heart failure management has been steered by the use of durable left ventricular assist devices (LVADs). This treatment option for a particularly complex population, whose mortality rate is as high as 50% within a year of diagnosis, has become widespread.¹⁾

During the 1990s, the pain was conceived as the “fifth vital sign.” Thereafter, an increase in the sales of opioids was observed with a subsequent rise in opioid-related mortality.²⁾ In 2016, the Centers for Disease Control and Prevention reported that drug overdose deaths nearly tripled from 1999 to 2014, with opioids being the primary cause.³⁾ Post-operative pain following device implant is typically managed with the opioid analgesics, but the impact of this therapy upon patient outcomes remains unexplored.

LVAD patients have rigorous requirements for self-management, which include driveline care and alarm troubleshooting. Additional responsibility may be the management of their pain control, which directly impacts their activities of daily living and quality of life.⁴⁾ Aside from the post-operative use, a more recent concern is the chronic use of these medications given increasing patients’

survival.

Opioids are frequently administered for symptoms related to patients’ cardiovascular conditions, comorbidities, or palliative care.⁵⁾ Past studies suggested that the use of specific analgesic agents can negatively affect post-operative mortality.²⁾ In the environment of an ongoing opioid epidemic, we recognize the importance of placing this finding into the context of our LVAD cohort. This study aimed to investigate the association between the use of opioids and clinical outcomes during LVAD supports.

Methods

Patient selection: After approval from the Institutional Review Board, electronic medical records of all patients implanted with durable LVADs from January 2014 to December 2017 were included in this retrospective study. Those patients were divided into two groups by the use of opioid at post-LVAD 3 months (baseline) and followed for 1 year from the baseline (Figure 1). All patients in the opioid group continued the opioid therapy. Patients who discontinued the opioid and those who initiated the opioid during the observational period were excluded and not en-

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Figure 1. Study schema. RHC indicates right heart catheterization, and LVAD, left ventricular assist device.

rolled in this study.

Opioid use: At our center, opioids are utilized to manage pain and heart failure congestive symptoms during LVAD supports. Upon hospital discharge, oxycodone or hydrocodone/acetaminophen are typically prescribed if needed.

Data collection: In addition to the baseline characteristics including hemodynamics data obtained by right heart catheterization at catheter laboratory room within 1 week before LVAD implantation, data of invasive hemodynamics performed within 1 year from the baseline were also collected. In our institute, hemodynamic assessments were routinely undergone at clinically stable conditions based on the ISHLT guidelines recommendation. The incidence of gastrointestinal bleeding (GIB), stroke, sepsis, driveline infection, pump thrombosis, and death during the 1 year observational period was also collected. The definition of these adverse events aligned with the INTERMACS descriptions.

Statistical analyses: Statistical analyses were performed with SPSS Statistics 22 (SPSS Inc, Armonk, IL, USA). Two-sided P -values of < 0.05 were considered statistically significant. Continuous variables were expressed as mean and standard deviation or median (25% quartile, 75% quartile), considering their distribution.

Event-free survival rates were assessed by using the Kaplan-Meier analysis and compared between groups using the log-rank test. Multivariate logistic regression analyses were performed to investigate the impacts of opioid use on GIB and sepsis adjusted for other baseline characteristics with $P < 0.05$ in the univariate analyses.

Results

Baseline characteristics: Of all, among 184 patients who received LVAD implantation, 19 patients who discontinued the opioid use during the study period and 29 patients who initiated the opioid use during the study period were excluded. As a result, 136 patients were enrolled in this study.

Demographic characteristics are summarized in Table I. Overall, age was 57 (48, 66) years old and 69% were male. Most of the patients (86%) received LVAD implantation as DT. In assessing the 136 patients, 77 (57%) were in the opioid group. Among the opioid group, specific opioid medications were hydrocodone/acetaminophen

(54), tramadol (11), hydromorphone (2), oxycodone (3), oxycodone/acetaminophen (5), fentanyl (1), and acetaminophen/codeine (1).

The opioid group was younger (54 versus 64 years, $P = 0.001$), exhibited a higher body mass index (30.8 versus 28.0, $P = 0.023$), contained fewer males (60% versus 81%, $P = 0.005$), and involved less incidence of atrial fibrillation compared with the no opioid group (30% versus 47%, $P = 0.018$). There were no statistically significant differences between the two groups in preoperative laboratory and hemodynamics data ($P > 0.05$ for all).

Trends of laboratory data: Laboratory data were collected at baseline and 3 months later (Table II). Hemoglobin and albumin levels tended to be lower in the opioid group compared with the non-opioid group ($P = 0.087$ and $P = 0.081$, respectively). C-reactive protein concentration was significantly higher at baseline ($P = 0.001$) and remained higher ($P = 0.051$) in the opioid group. Prothrombin time with international ratio remained unchanged between the two groups. Bilirubin and creatinine levels were comparable between the two groups.

Hemodynamic data: Of all, 30 patients were excluded from the hemodynamic analyses because of lack of RHC data or their unstable condition. Central venous pressure and pulmonary capillary wedge pressure were significantly higher in the opioid group ($P \leq 0.001$ and $P = 0.011$, respectively; Table III). The cardiac index was statistically comparable between the two groups ($P = 0.13$).

Freedom from events: One year survival was lower in the opioid group than the no opioid group, although the difference did not reach statistical significance (83% versus 90%, $P = 0.27$; Figure 2A). Similarly, the lower freedom from adverse events in the opioid group compared with the no opioid group was statistically not different (31% versus 46%, $P = 0.31$; Figure 2B).

Incidences of individual adverse events: The incidences of GIB and sepsis were statistically higher in the opioid group compared with the no opioid group ($P = 0.043$ and $P = 0.036$, respectively; Figure 3). The incidences of stroke, driveline infection, and pump thrombosis were statistically comparable between the two groups ($P > 0.05$ for all).

Predictors of GIB and sepsis among baseline characteristics: Opioid use was a significant predictor of GIB even after the adjustment for variables significant in the univariate analyses ($P < 0.05$; Table IV). Opioid use and older age were both significant predictors of sepsis ($P < 0.05$ for both; Table V).

Discussion

Hemodynamics: One mechanism that may explain the worsening hemodynamics in the opioid group is the common complication of urinary retention. This condition results from the partial inhibition of the parasympathetic nerves that innervate the bladder. Also, sympathetic overstimulation can increase the tonicity of the urinary sphincter, leading to increased resistance in the outflow tract of the bladder.⁸⁾ The resulting increase in pressure within the urinary tract can cause kidney damage and, consequently, fluid retention.

Table I. Baseline Characteristics

	Total (n = 136)	Opioid (n = 77)	No opioid (n = 59)	P value
Demographics				
Age, years	57 (48, 66)	54 (47, 62)	64 (54, 69)	0.001*
Body mass index	29.5 (25.3, 35.7)	30.8 (26.3, 37.1)	28.0 (24.4, 35.1)	0.023*
Male	94 (69%)	46 (60%)	48 (81%)	0.005*
Destination therapy	117 (86%)	64 (83%)	53 (90%)	0.43
Device				
Axial flow LVAD	68 (50%)	42 (55%)	26 (44%)	0.15
Centrifugal LVAD	68 (50%)	35 (45%)	33 (56%)	0.15
Comorbidity				
Ischemic etiology	42 (31%)	22 (29%)	20 (34%)	0.32
Hypertension	72 (53%)	39 (51%)	33 (56%)	0.26
Diabetes mellitus	46 (34%)	29 (38%)	17 (29%)	0.22
Atrial fibrillation	51 (38%)	23 (30%)	28 (47%)	0.018*
History of stroke	20 (15%)	13 (17%)	7 (12%)	0.31
History of ventricular tachyarrhythmia	48 (35%)	29 (38%)	19 (32%)	0.37
Chronic obstructive pulmonary disease	32 (24%)	21 (27%)	11 (19%)	0.19
Obstructive sleep apnea	27 (20%)	16 (21%)	11 (19%)	0.51
Chronic kidney disease	39 (29%)	24 (31%)	15 (25%)	0.34
Preoperative laboratory data				
Hemoglobin, g/dL	10.5 (9.4, 11.5)	10.6 (9.3, 11.7)	10.4 (9.2, 11.9)	0.64
Albumin, mg/dL	3.5 (3.2, 3.8)	3.4 (3.1, 3.7)	3.6 (3.3, 3.8)	0.31
Total bilirubin, mg/dL	0.9 (0.6, 1.7)	0.9 (0.7, 1.4)	1.0 (0.5, 1.8)	1.0
Creatinine, mg/dL	1.3 (1.0, 1.6)	1.3 (1.1, 1.7)	1.1 (1.0, 1.5)	0.88
C-reactive protein, mg/dL	8.7 (5.4, 12.4)	8.4 (3.2, 13.2)	8.7 (4.9, 12.9)	0.53
Preoperative hemodynamics				
Central venous pressure, mmHg	13 (8, 17)	12 (8, 16)	13 (5, 18)	0.88
Pulmonary capillary wedge pressure, mmHg	25 (20, 31)	25 (17, 30)	26 (20, 31)	0.57
Cardiac index, L/min/m ²	1.94 (1.50, 2.40)	1.90 (1.58, 2.25)	2.09 (1.54, 2.51)	0.80

LVAD indicates left ventricular assist device. * $P < 0.05$. Continuous variables were compared by the Mann-Whitney U test. Categorical variables were compared by Fisher's exact test.

Table II. Trends in Laboratory Data at 3 Months (Baseline) and 6 Months (Follow-Up) Following LVAD Implantation

	Opioid (n = 77)	No opioid (n = 59)	P value
Hemoglobin, g/dL			
Baseline	10.7 ± 1.6	11.1 ± 1.4	0.11
Three months later	10.1 ± 1.9	11.1 ± 2.3	0.087
Albumin, mg/dL			
Baseline	3.9 ± 0.6	4.0 ± 0.5	0.30
Three months later	3.8 ± 0.5	4.1 ± 0.5	0.081
Total bilirubin, mg/dL			
Baseline	0.6 ± 0.5	0.7 ± 0.4	0.46
Three months later	0.6 ± 0.4	0.7 ± 0.4	0.53
Creatinine, mg/dL			
Baseline	1.3 ± 0.3	1.3 ± 0.4	0.81
Three months later	1.5 ± 0.7	1.4 ± 0.5	0.27
C-reactive protein, mg/dL			
Baseline	13.0 (7.0, 38.0)	0 (0, 6.8)	0.001*
Three months later	25.0 (7.0, 72.0)	0 (0, 27.5)	0.051
INR			
Baseline	2.13 ± 0.80	2.08 ± 0.57	0.69
Three months later	2.12 ± 0.76	2.13 ± 0.67	0.94

INR indicates prothrombin time with international ratio. * $P < 0.05$. Variables were compared by using unpaired t -test or Mann-Whitney U test as appropriate.

Another explanation is that those with worse hemodynamics may tend to receive opioid to manage their

heart failure symptoms due to pulmonary and systemic congestions.

Table III. Comparison in Invasively Measured Hemodynamic Variables Performed during the Observational Period

	Opioid (n = 60/77)	No opioid (n = 46/59)	P value
Central venous pressure, mmHg	11.8 ± 6.0	7.9 ± 4.3	< 0.001*
Pulmonary capillary wedge pressure, mmHg	17.1 ± 8.5	13.4 ± 6.1	0.011*
Cardiac index, L/minute/m ²	2.36 ± 0.47	2.18 ± 0.35	0.13

* $P < 0.05$. Variables were compared by unpaired t -test. **Figure 2.** Survival rate (A) and freedom from adverse events (B) during 1 year study period between the opioid group and the no opioid group. Both curves were compared by using log-rank test. **Figure 3.** Rates of individual adverse events. GIB indicates gastro-intestinal bleeding; DLI, driveline infection; and PT, pump thrombosis. * $P < 0.05$. Variables were compared between two groups by using Fischer's exact test.

Laboratory data: We found that the opioid group tended to have lower albumin and hemoglobin levels. The explanation for the former lies in the fact that opioids can suppress appetite, resulting in a decrease in food intake and, by extension, albumin levels. This occurs via the activation of opioid receptors in the GI tract, slowing down bowel movements and causing constipation.⁹⁾ As a result, the appetite of the opioid user is suppressed, causing albumin levels to decrease.

The trend of lower hemoglobin levels in the opioid group can be explained by the common occurrence of OP-induced endocrinopathy. Long-term use of opioids is known to create a deficiency in hypothalamic-pituitary-gonadal axis, which results in a decreased production of

sex hormones. This can result in anemia, with a consequent drop in hemoglobin. Additionally, men with hypogonadism produce fewer red blood cells, another way that hemoglobin may decrease.¹⁰⁾

Another explanation is that the patients with more advanced cardiac cachexia who have progressed anemia and hyponatremia might tend to receive opioid.

Sepsis: Prior literature offers a few possible explanations for the increased sepsis in the opioid group. Both the chronic use of morphine, an opioid, and the subsequent withdrawal result in a compromised immune system.¹²⁾ Several studies in murine models have shown that morphine can induce microbial dysbiosis and gut barrier compromise, promoting the expansion of mostly gram-positive commensal flora.¹³⁾ The compromised mucosal barrier allows for bacterial translocation, resulting in localized gut and systemic inflammation, a hallmark of sepsis. Other studies have shown that morphine causes gram-negative bacteria to escape the GI tract, leading to sepsis along with increased susceptibility to endotoxins. This series of events is opioid receptor-mediated as it is blocked by naltrexone, an opioid receptor antagonist.¹⁴⁾

One study showed that morphine induces a virulent phenotype in *P. aeruginosa*, which is capable of inducing lethal gut-derived sepsis in mice.¹⁵⁾ Lipopolysaccharide, an endotoxin released by gram-negative bacteria, activates the complement system and causes macrophages to release pro-inflammatory cytokine, which causes chronic inflammation and sepsis. In cases where bacterial clearance is low, such as in chronic morphine regimens, lipopolysaccharides can rise to levels that cause septic shock, in part due to the translocation and proliferation of microbes.^{16,17)} A clinical study of almost 6,000 patients with sepsis

Table IV. Predictors of GIB among Baseline Characteristics

	Univariate analyses		Multivariate analyses	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, years	1.04 (1.00-1.08)	0.045*	1.05 (1.01-1.10)	0.028*
Body mass index	1.00 (0.95-1.05)	0.99		
Female	2.19 (0.98-4.92)	0.057	2.71 (1.05-6.99)	0.039*
Destination therapy	3.08 (0.70-13.70)	0.14		
Axial flow LVAD	0.86 (0.39-1.86)	0.69		
Ischemic etiology	3.08 (1.37-6.94)	0.006*	3.68 (1.48-9.17)	0.005*
Diabetes mellitus	1.06 (0.47-2.40)	0.89		
Atrial fibrillation	1.65 (0.75-3.63)	0.21		
History of stroke	0.47 (0.13-1.73)	0.26		
Chronic kidney disease	1.48 (0.64-3.38)	0.36		
INR at baseline	0.86 (0.48-1.56)	0.62		
Opioid use	2.22 (0.96-5.11)	0.061	2.75 (1.06-7.13)	0.038*

LVAD indicates left ventricular assist device; and CI, confidence interval. * $P < 0.05$ by logistic regression analyses with endpoint of GIB.

Table V. Predictors of Sepsis among Baseline Characteristics

	Univariate analyses		Multivariate analyses	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, years	1.04 (1.00-1.08)	0.029*	1.06 (1.01-1.10)	0.013*
Body mass index	0.96 (0.91-1.02)	0.17		
Female	1.77 (0.78-4.04)	0.18		
Destination therapy	1.01 (0.409-2.60)	0.98		
Axial flow LVAD	0.85 (0.38-1.88)	0.69		
Ischemic etiology	2.13 (0.93-4.76)	0.075	1.69 (0.69-4.13)	0.25
Diabetes mellitus	2.40 (1.06-5.41)	0.035*	2.07 (0.87-4.96)	0.10
Atrial fibrillation	1.37 (0.61-3.06)	0.45		
History of stroke	1.45 (0.51-4.15)	0.49		
Chronic kidney disease	0.94 (0.39-2.27)	0.89		
INR at baseline	0.52 (0.25-1.05)	0.11		
Opioid use	2.37 (1.00-5.60)	0.050	3.47 (1.32-9.14)	0.012*

LVAD indicates left ventricular assist device; and CI, confidence interval. * $P < 0.05$ by logistic regression analyses with endpoint of sepsis.

found that opioid-treated patients had a significantly higher risk of death at 28 days, consistent with the results of the aforementioned animal studies.¹⁸⁾

GI complications: GIB is the most common adverse event among VAD patients.⁵⁾ The need for anticoagulation therapy complicates the management of GIB.

Regarding GI tract complications with opioids in a general population, symptoms may include constipation, often accompanied by straining. This may lead to hemorrhoids, which, in turn, can cause GIB. Additionally, opioid-induced constipation has been shown to negatively affect patients' abilities to carry out their activities of daily living.^{19,20)}

Peptic ulcers are the greatest contributor to upper GIB. Non-steroid anti-inflammatory drugs have been found to cause peptic ulcers, so recommendations are often made to use tramadol, which is an opioid. However, one study found that, in patients hospitalized for peptic ulcer disease, both tramadol and non-steroid anti-inflammatory drugs increased mortality to a comparable level.¹⁸⁾

Another mechanism is the hemodynamics abnormality. In our study, opioid use was associated with abnormal

hemodynamics including systemic congestion, although whether the causality between the opioid use and abnormal hemodynamics remains unknown. Systemic congestion seems to have association with the activation of inflammatory and angiogenesis systems that develops arteriovenous malformation and successive GIB.

Adverse event prevention: With opioid use, negative effects may include a decrease in mobility with a resulting decrease in circulatory perfusion, a reduction in lung expansion, and an impaired immune system. These negative effects could lead to infection and/or sepsis, one of the leading causes of mortality in patients placed on LVAD support. Limiting device-related infections is an important consideration to improve survival, and patients with LVADs should be well educated on the importance of infection prophylaxis.⁷⁾ This is especially significant in light of literature showing a possible higher mortality rate in patients on prescription opioids who are diagnosed with sepsis.¹⁸⁾ The best means of infection prophylaxis in LVAD patients is protecting the percutaneous driveline from the movement at the exit site, which can disrupt tissue ingrowth around it.^{1,7)} Thus, patient understanding of the importance of exit site care should be ensured, and

family members should be educated and recruited to help if possible. Additionally, promoting mobility in general with the possible inclusion of physical therapy or cardiac rehab may prevent these complications.

Limitations: This is a retrospective analysis, and we recognize the inherent limitations. Our documentation lacked details such as the possible causative factors for the adverse events. For instance, we did not identify the pathogen responsible for the infections. Additionally, we did not investigate the impact of type, dose, and duration of the opioids. We also did not explore the nuances of long-term opioid addiction/abuse and its effect on outcomes post-LVAD implantation. As shown in Table I, our cohort might be relatively unique with high destination therapy indication due to the geographic nature, and our findings might not simply be adopted in other institutes and countries. Finally, we did not investigate the causality of opioid use on comorbidities and just investigated the association. There were no statistically significant associations between the opioid use and the incidences of stroke, driveline infection, and pump thrombosis, but the impact of opioid use on these comorbidities still remains a future concern.

Conclusion

The opioid use might have an association with worse hemodynamics and comorbidities including GIB and sepsis. The causality of opioid on each comorbidity and detailed mechanism of their relationship remain a future concern.

Disclosure

Conflicts of interest: None.

Institution at which the work was performed

University of Chicago Medicine

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